INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/24751

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : G 01 N 33/00, 48
US CL : 702/19,27
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 702/19,27

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	Schneider G. Peptide design by artificial neural networks and computer-based evolutionary search . Biochemistry, October 13, 1998, Vol. 95, Issue 21, 12179-12184	1-52 --- 82
X --- Y	US 2002/0177170 (LUO et al) 11/28/2002	1-52 --- 82
X --- Y	US 20020119492 A1 (CHIRINO et al), August 29, 2002	1-52 --- 82

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"B" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
02 December 2005 (02.12.2005)

Date of mailing of the international search report
21 FEB 2006

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
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Alexandria, Virginia 22313-1450
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Authorized officer
Michael Borin
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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-52 and 82

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.

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BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

Group I, claims 1-52,73-98 drawn to method for constructing variant set for antibody. See also, an election of species requirement below.

Group II, claims 66, drawn to variant set having no threshold value for a property, or components thereof, obtained according to claim 1,2 or 6.

Group III, claims 59-62,65 drawn to nucleic acids encoding variants obtained according to claim 1 or 2 or 6.

Group IV, claims 67-70, drawn to cells containing variants obtained according to claim 1 or 2, or 6 or containing polynucleotides encoding therefor.

Group V, claims 53-55, drawn to variant set having property of that exceeds a predetermined value, or components thereof.

Group VI, claim 56-58, drawn to nucleic acids encoding variants having property of that exceeds a predetermined value.

Group VII, claim 64, drawn to variant set of less than predetermined value, or components thereof or components thereof, obtained according to claim 4.

Group VIII, claim 63, drawn to nucleic acids encoding variants obtained according to claim 4.

Group IX, claims 71, 72 drawn to cells containing variants obtained according to claim 4 or containing polynucleotides encoding therefor.

Group X, claims 98-100, drawn to method of treatment. See also an election of species requirement below.

Group XI, claims 101-118, drawn to method of weighting selection rules.

Group XII, claim 119, drawn to computer software.

Group XIII, claim 120, drawn to computer system.

Further, this application contains claims directed to more than one species of the generic invention. The species identified below are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows:

For Group I :

I.1. Measuring property according to claim 82;
I.2. Measuring property according to claims 83,84 ;
I.3. Measuring property according to claims 85,86;
I.4. Measuring property according to claims 87,88;
I.5. Measuring property according to claims 89,90 ;
I.6. Measuring property according to claims 91,92 ;
I.7. Measuring property according to claims 93,94 ;
I.8. Measuring property according to claims 95-97.

For Group X:

X.1 . Treatment of diseases caused by pathogenic organism;
X. 2. Treatment of diseases caused by a virus;
X. 3. Treatment of diseases caused by cancer.

The inventions listed as Groups I-XIII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Groups directed to "variants" is the technical feature that links Groups I to XIX. The claims of the Groups directed to variants are not the contribution over the prior art because they are suggested by references teaching any sets of antibody derivatives. For example, such sets of antibody derivatives are taught in US 5,843,708 directed to chimeric antibodies.. Therefore, the lack of unity is present because the linking technical feature is not a "special technical feature" as defined by PCT Rule 13.2. Further, the variants of Groups II, V, VII are not addressed as having common core structure, and are clearly distinct as their structure satisfies different functional requirements. Same for groups directed to corresponding nucleic acids or cells.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
BRETT A. LOVEJOY
JONES DAY
222 EAST 41ST STREET
NEW YORK, NY 10017-6702

PCT

REC'D 23 FEB 2006
WIPO PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing (*day/month/year*)	21 FEB 2006
Applicant's or agent's file reference 11548-03-228	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US04/24751	30 July 2004 (30.07.2004)	01 August 2003 (01.08.2003)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): G01N 33/00, 48 and US Cl.: 702/19,27

Applicant

DNA TWOPOINTO INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☐ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☐ Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	02 December 2005 (02.12.2005)	Michael Borin Telephone No. ((571) 272-054

Form PCT/ISA/237 (cover sheet) (April 2005)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ on paper

☐ in electronic form

c. time of filing/furnishing

☐ contained in the international application as filed.

☐ filed together with the international application in electronic form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:
   - ☐ paid additional fees
   - ☐ paid additional fees under protest and, where applicable, the protest fee
   - ☐ paid additional fees under protest but the applicable protest fee was not paid
   - ☒ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
   - ☐ complied with
   - ☒ not complied with for the following reasons:

   See the lack of unity section of the International Search Report(Form PCT/ISA/210)

4. Consequently, this opinion has been established in respect of the following parts of the international application:
   - ☐ all parts.
   - ☒ the parts relating to claims Nos. 1-52 and 82

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 82	YES
	Claims 1-52	NO
Inventive step (IS)	Claims NONE	YES
	Claims 1-52,82	NO
Industrial applicability (IA)	Claims 1-52,82	YES
	Claims NONE	NO

2. Citations and explanations:

Please See Continuation Sheet

Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

V. 2. Citations and Explanations:
Claims 1-52 lack novelty under PCT Article 33(2) as being anticipated by Chirino et al. (US 20020119492) or Schneider et al or Peizi et al. (US 20020177170) .

The instant claims are directed to method for constructing a variant set for an antibody of interest comprising generating a variant set containing substitutions in a plurality positions of the antibody, measuring properties of variants in the variant set, correlating structure changes with activity and redefining the variant set. Note, that the "antibody sequence space" means merely a set of substitutions considered for a plurality of positions in an antibody sequence.
Methods of computational modeling of polypeptide variants are well known in the art; the following references are exemplary.

Chirino et al. (US 20020119492) teach constructing variant sets for various proteins of interest. Proteins of interest include, antibodies, ligands, etc. Paragraphs [0060-0062] . The method comprising: a) inputting a protein backbone structure with variable residue positions of a target protein into a computer; b) computationally generating a set of primary variant amino acid sequences. See claims 1,2, for example. Providing potential substitutions for plurality of positions generates secondary libraries (i.e., a "sequence space"). See paragraphs , for example [0080-0082,0119-0121]. Potential sequences of interest are then tested to determine if its activity is similar to the target protein. Paragraph [0148]. Combining candidate variant secondary libraries creates tertiary library Paragraph [0208-0209] .

Schneider et al teach a method for peptide design by artificial neural networks comprising the steps of identification of a "seed peptide" with a desired activity, generation of variants selected from a physicochemical space around the seed peptide, synthesis and testing of this biased library, modeling of a quantitative sequence-activity relationship by an artificial neural network. See abstract.

Peizi et al. (US 20020177170) teach methods for designing antibody library.
The procedures involve the exploration of sequence, structure and functional spaces and the evaluation of the relationships among them (FIGS. 1A-D, 1E-H, 2A-C). Starting point can be either a lead structure or a lead sequence or both, if available. The procedure systematically explores both the sequence space and structure space in order to identify variant profiles optimized for functional screening. There are three modes of information exchange: i) separate evaluation of information in sequence and/or structure space and then combined, ii) consecutive evaluation from sequence to structure, or from structure to sequence, or iii) from sequence or structure alone. While the sequence design can be explored in sequence and structure spaces separately (two separate cycles), the variant profiles from these two separate cycles can be compared and combined in order to arrive at the optimal overall variant profile with good consensus variant profile that is likely to produce strong candidates in the functional screen. The two filtering and refining cycles in sequence and structure spaces are further linked during the filtering and evaluative steps because the variant profiles arrived by each cycle are compared and/or passed to the other cycle for further refinement. For the sequence-derived variant profile, it is structurally

Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

evaluated on a known template in structure space in order to rank and refine the variant profile. Conversely, the structure-derived variant profile can be passed on to the sequence space to evaluate if they belong to the same superfamily of the hit or variant library or for comparison and partitioning to control the final library size. In sequence space, the goal is to determine the variant profile that is optimized for the target function. The cycle begins with the identification of the hit library through database sequence search and alignment using the sequence profile. In structure space, the goal also is to determine the variant profile optimized for the target function but starting with one structure or an ensemble of structures and then scoring the sequences based on the average of the ensemble of structures. The cycle begins with a set of structures and associated sequences that can be computationally screened and evaluated using a scoring function. One result of the design protocol is the optimal variant profile. It embodies the results of both the sequence and structure evaluations so that evolutionary and structural preferences are incorporated into the design. Subsequent steps in the functional space aim to evaluate and refine this profile, and, if necessary, modify earlier steps, so that cyclic enrichment of the resulting library can be accomplished at various steps in the design protocol. See paragraphs [565-579].

Claim 82 lacks an inventive step under PCT Article 33(3) as being obvious over Chirino et al. (US 20020119492) or Schneider et al or Peizi et al. (US 20020177170) Selection of a particular property of interest, such as those claimed in claim 82, would be within perview of an artisan as a part of routine optimization